A phase 1/2 study of AVZO-023, a next-generation selective cyclin-dependent kinase 4 inhibitor (CDK4i), as a single agent and in combination with AVZO-021, a selective cyclin-dependent kinase 2 inhibitor (CDK2i), and/or endocrine therapy in patients with breast cancer

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FOR ADDITIONAL INFORMATION

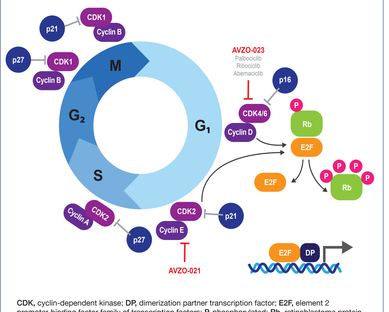
NCT06998407

Poster #2267

BACKGROUND[1-9]

Aberrant Cell Cycle Regulation Is Common in HR+ Breast Cancer

- The cyclin D1-CDK4/6-pRB pathway drives the cell cycle transition from cell growth (G1) to DNA synthesis (S) and is often deregulated in hormone receptor-positive (HR+) breast cancer (**Figure 1**)[1,2]
- Several CDK4/6 inhibitors (CDK4/6i) have been approved by the FDA for use in combination with endocrine therapy (ET) in locally advanced or metastatic HR+/hormone epidermal growth factor receptor 2-negative (HER2-) breast cancer[3]

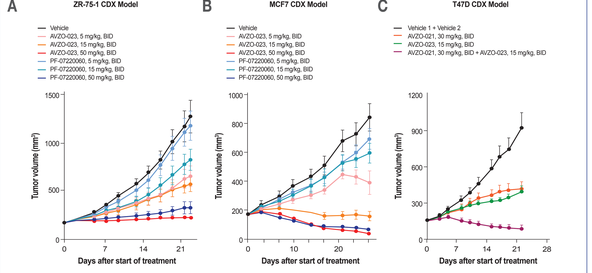


CDK, cyclin-dependent kinase; **DP**, dimerization partner transcription factor; **E2F**, element 2 promoter-binding factor family of transcription factors; **P**, phosphorylated; **Rb**, retinoblastoma protein.

Figure 1. Inhibition of CDK4 halts the cell cycle in the G1 phase, preventing cancer cells from dividing and proliferating.[1,2,4]

AVZO-023 Is a Potent CDK4i With High Selectivity Over CDK6 and Robust Antitumor Activity

- AVZO-023 demonstrated robust CDK4/CCND1 inhibition with high selectivity over CDK6 in vitro[9]
- In two ER+ breast cancer models, AVZO-023 demonstrated dose-dependent tumor growth inhibition (**Figure 2A,B**) and exhibited a favorable toxicity profile in preclinical studies[9]
- Combining AVZO-023 with AVZO-021 (a highly selective CDK2i) enhanced tumor growth inhibition compared with either agent alone in an ER+ breast cancer model (**Figure 2C**)[9]



Data points represent group mean; error bars represent the standard error of the mean
BID, twice per day
AVZO-023 was previously known as ARTS-023

Figure 2. AVZO-023 (ARTS-023) Demonstrates Antitumor Activity in ER+ Breast Cancer Models.[9] AVZO-023 inhibited tumor growth in the ZR-75-1 CDX model (**A**). AVZO-023 inhibited tumor growth in the MCF7 CDX model (**B**). AVZO-023 + AVZO-021 inhibited tumor growth in T47D xenografts more than either agent alone (**C**).

Targeting CDK4 and CDK2 to Overcome Limitations of CDK4/6i Therapy

- Clinical trials have shown meaningful improvements in progression-free survival (PFS) and overall survival (OS) with CDK4/6i; however, the clinical utility of CDK4/6i is limited by hematological toxicity and CDK2-mediated resistance[3-5]
- Combining a selective CDK4i with a selective CDK2i may lead to a more durable response and disease control by maximizing CDK4 target coverage, sparing CDK6i-dependent hematologic toxicity, and overcoming CDK2-driven resistance mechanisms[6-8]

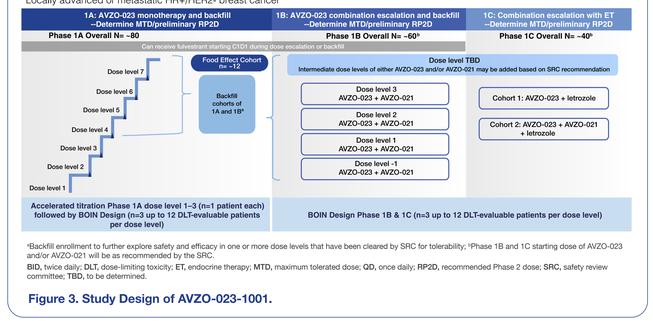
AVZO-023-1001 STUDY DESIGN[10,11]

Study Objectives and Patient Population

- Patients with locally advanced or metastatic **HR+/HER2- breast cancer** will be enrolled
- The goal of the Phase 1 AVZO-023-1001 study is to determine the preliminary recommended Phase 2 dose (**RP2D**) and/or the maximum tolerated dose (**MTD**) of AVZO-023 as monotherapy and combination therapy
- Phase 1 will also assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of AVZO-023 as monotherapy and in combination therapy

Study Design

- Part A will evaluate AVZO-023 (BID) monotherapy in an accelerated titration for the first 3 dose levels followed by a BOIN design for dose escalation
  - A separate food effect cohort will be included
- Part B will evaluate AVZO-023 (BID) + AVZO-021 (QD), and Part C will evaluate AVZO-023 + letrozole (ET) ± AVZO-021 using a BOIN design for dose escalation
- Patients in Part A or B can receive fulvestrant during dose escalation or during backfill starting at cycle 1, day 1
- The preliminary RP2D for AVZO-023 monotherapy and AVZO-023 + ET ± AVZO-021 will be selected based on the totality of the data from Parts A, B, and C
- Part A will enroll ~80 patients, Part B will enroll ~60 patients, and Part C will enroll ~40 patients



[a]Backfill enrollment to further explore safety and efficacy in one or more dose levels that have been cleared by SRC for tolerability; [b]Phase 1B and 1C starting dose of AVZO-023 and/or AVZO-021 will be as recommended by the SRC.
BID, twice daily; **DLT**, dose-limiting toxicity; **ET**, endocrine therapy; **MTD**, maximum tolerated dose; **QD**, once daily; **RP2D**, recommended Phase 2 dose; **SRC**, safety review committee; **TBD**, to be determined.

Figure 3. Study Design of AVZO-023-1001.

KEY ELIGIBILITY CRITERIA[10,11]

Key Inclusion Criteria

- ≥18 years of age
- Histologically or cytologically confirmed locally advanced or metastatic HR+/HER2- breast cancer with the following **prior therapy:**
  - Prior therapy with CDK4/6 inhibitor(s) and ET in the advanced or metastatic setting
    - Up to 2 CDK4/6 inhibitors, with no more than 1 in the advanced or metastatic setting
    - Any number of prior ET without progression within 6 months of initial ET in the advanced or metastatic setting
  - Up to 3 lines of chemotherapy (including ADCs) in the advanced or metastatic setting
- Measurable disease per investigator using RECIST v1.1[a]
- Eastern Cooperative Oncology Group (ECOG) Performance Status ≤1 and life expectancy >3 months

Key Exclusion Criteria

- Prior treatment with selective investigational CDK inhibitors (CDK2, CDK4, CDK2/4, CDK2/4/6)
- Progression during or within 12 months of completing CDK4/6i therapy in the adjuvant setting
- Known active brain metastasis[b]
- Received radiotherapy with a limited field of radiation for palliation within 7 days of the first dose on study[c]
- Unresolved toxicities from prior therapy greater than Grade 1 (per CTCAE version 5.0) (with exceptions of alopecia, vitiligo, and Grade ≤2 peripheral neuropathy) prior to the first dose on study[d]
- Confirmed by investigator loss of function mutation or deletion of *Rb1* gene

[a]Measurable disease is preferred in Phase 1 dose escalation and is required for backfill enrollment; for patients with HR+/HER2- breast cancer enrolled in dose escalation, bone only disease is allowed. [b]Have either previously untreated intracranial central nervous system (CNS) metastasis or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions. [c]Except for patients receiving whole brain radiotherapy, which must be completed at least 4 weeks prior to the first dose of study treatment. Patients must have recovered from all radiation-related toxicities, not require corticosteroids, and not have active radiation pneumonitis. [d]Patients who experienced a Grade ≥2 adverse event (AE) at event onset, but who are asymptomatic/stable on maintenance therapy at the time of evaluation for eligibility, will be considered eligible.

STUDY ENDPOINTS[10,11]

Primary Endpoints

- **Safety and Tolerability:** Number of patients with dose-limiting toxicities (DLTs) during the first cycle, incidence and severity of treatment-emergent adverse events (AEs) and serious AEs
- Changes including hematology and chemistry values, vital signs, electrocardiograms, dose interruptions, reductions, and dose intensity
- **MTD or preliminary RP2D** of AVZO-023 as both monotherapy and in combination therapy

Secondary Endpoints

- **Preliminary Antitumor Activity:** Assess activity, including objective response rate, duration of response, clinical benefit rate, disease control rate, PFS, and OS, of AVZO-023 as monotherapy and in combination therapy using RECIST v1.1, as assessed by the investigator
- **Pharmacokinetics:** To characterize the PK of AVZO-023, including maximum observed plasma concentration, time to maximum observed plasma concentration, elimination half-life, area under the plasma concentration-time curve (AUC) from time 0 to last measurable concentration, AUC from time 0 to infinity, AUC from time 0 to the end of the dosing period, and apparent clearance

The study is active and will enroll patients at approximately 50 centers across North America, Europe, and the Asia-Pacific region.

The latest information on this study can be found at ClinicalTrials.gov, reference number NCT06998407.

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